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(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas & Ohlstein (2001). Trends Cardiovasc. Med., 10: in press).

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: **131; 10-12**) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypersensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al.Brain Research* 923 (2001) 120-127.

Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

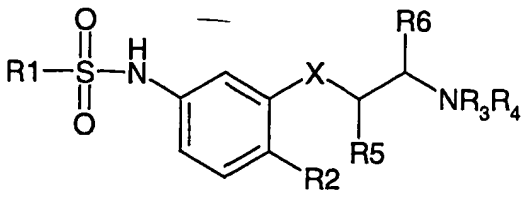
In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

R1 is benzofuranyl, benzothiazoyl, benzoxazoyl, benzimidazoyl, oxazoyl, indoyl, triazinyl, imidazoyl, pyrimidinyl, naphthyridinyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl substituted or unsubstituted by one, two, three, four or five of any of the following: halogen, CF_3, OCF_3, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, $CONR_7R_8$, NR_9R_{10}, SC_{1-6} alkyl, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl);

R_2 is hydrogen, halogen, CF_3, CN or C_{1-4} alkyl;

R_3, R_4, R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_5, R_6, R_9, and R_{10} are independently hydrogen or C_{1-6} alkyl;

X is O, S, or CH_2;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Preferably R1 is pyrimidinyl, substituted or unsubstituted by one, two, or three of any of the following: C_{1-6} alkoxy, SC_{1-6} alkyl.

Preferably R_2 is halogen.

Preferably R_3 is C_{1-6} alkyl.

Preferably R_4 is C_{1-6} alkyl.

Preferably R_5 is hydrogen.

Preferably R_6 is hydrogen.

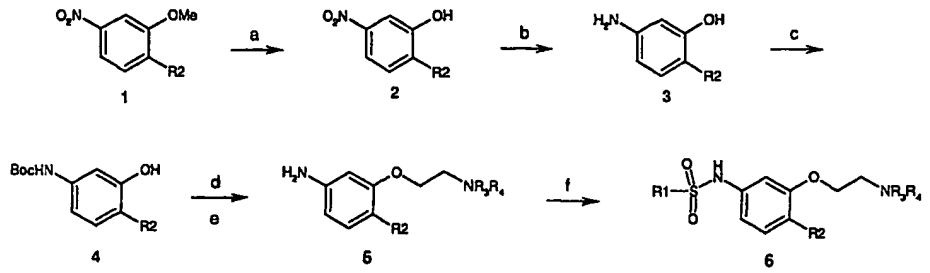
Preferably X is O.

Preferred Compounds are:

4-Methoxy-2-propylsulfanyl-pyrimidine-5-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide.

Compounds of Formula I may be prepared as set forth in Scheme 1.

Scheme 1



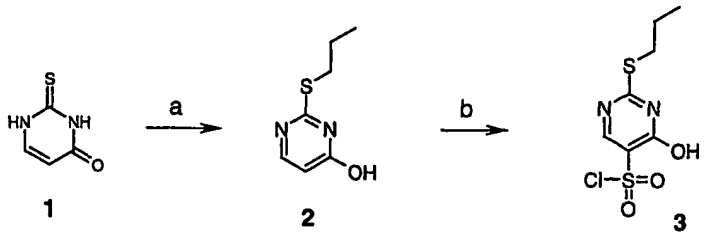
1 2 3 4 5 6

Conditions: a) 48% hydrogen bromide, acetic acid; b) hydrogen (50 psi), platinum on carbon, ethyl acetate; c) di-*tert*-butyldicarbonate, tetrahydrofuran, reflux; d) $ClCH_2CH_2NR_3R_4$-hydrochloride, potassium carbonate, water/1,2-dimethoxyethane, reflux; e) 6 N hydrogen chloride; f) R_1-SO_2Cl, chloroform, ambient temperature. R_1, R_2, R_3, and R_4 are as defined in Formula (I).

For example, acid-mediated demethylation of anisoles **1** gave phenols **2**. Hydrogenation of the nitro group provided anilines **3**, which were subsequently protected as their *tert*-butoxycarbonyl carbamates **4**. Alkylation of **4** with various dialkylaminoethyl chlorides, followed by removal of the nitrogen protecting group afforded anilines **5**. Subsequent sulfonylation of the anilines furnished the target compounds **6**.

Preparation of R_1-SO_2Cl is set forth in scheme 2:

Scheme 2



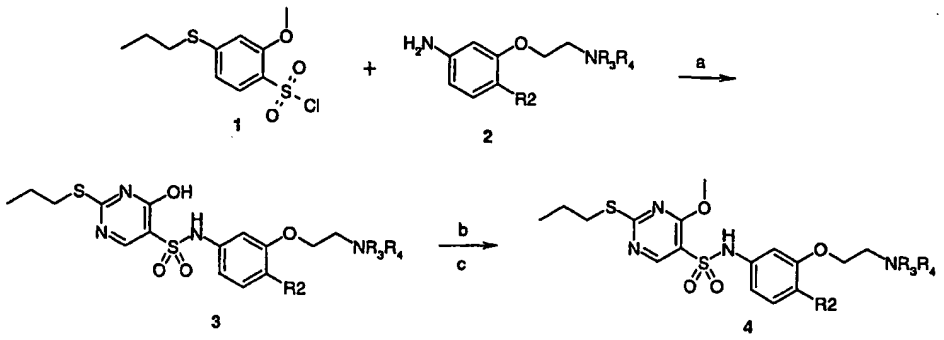
1 2 3

Conditions: a) 1-bromopropane, potassium carbonate, dimethylformamide; b) chlorosulfonic acid, reflux.

A number of optionally substituted benzenesulfonyl chlorides used in the synthesis of the title compounds were prepared. For example, alkylation of 2-thiouracil (1) with bromopropane furnished hydroxypyrimidine 2. Conversion to the desired sulfonyl chloride was accomplished by treating 2 with chlorosulfonic acid at reflux to provide 3.

The arylsulfonamide could also be manipulated to afford additional analogs as set forth in scheme 3.

Scheme 3



Conditions: a) phosphorus oxychloride, reflux; b) sodium methoxide, ambient temperature.

For example, sulfonylation of aniline 2 with sulfonyl chloride 1 gave sulfonamide 3. Conversion of the phenol hydroxy group to a methoxy was accomplished by treating 3 with phosphorus oxychloride at reflux, followed by sodium methoxide at ambient temperature to furnish the desired target compounds 4.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-

II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

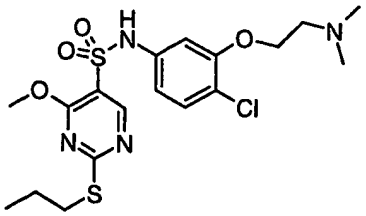
HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 10 nM – 10000 nM (example 1 Ki = 220 nM)

The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

4-methoxy-2-propylsulfanyl-pyrimidine-5-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide.



a) 2-Chloro-5-aminophenol

2-Chloro-5-nitroanisole (310 g, 1.7 mol) was taken up in a mixture of 48% HBr (1.5 L) and AcOH (1.2 L) and heated at reflux for 3 days. The dark solution was allowed to cool to room temperature, poured into ice water (10 L), and let stand for 3 h. The resultant dull yellow solid was filtered, washed with water, and dried in vacuo (230 g, 79%): mp 115-117 °C.

b) 2-Chloro-5-aminophenol

A solution of 2-chloro-5-nitrophenol (25 g, 0.14 mol) in ethyl acetate (150 mL) was treated with 5% Pt/C (250mg) and the mixture shaken under a hydrogen atmosphere (30 psi) for 4h. The mixture was filtered through Celite® and the residue washed well with hot ethyl acetate. The filtrate was treated with activated charcoal and re-filtered as above. Evaporation of the ethyl acetate gave a solid (19.8 g, 98%).

c) 4-Chloro-3-hydroxyphenylcarbamic acid tert-butyl ester

To a solution of 2-chloro-5-aminophenol (20 g, 0.14 mol) in THF (150 mL) was added a solution of di-*tert*-butyl dicarbonate (33 g, 0.15 mol) in THF (150 mL). The reaction was heated at reflux for 6 h, at which time it was allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue diluted with ether (500 mL) and washed with 1 M citric acid (2 x 300 mL). The aqueous washings were extracted with ether (300 mL) and the combined organics washed with brine (300 mL), dried ($MgSO_4$), and concentrated. The resultant brown solid was triturated with hexanes and dried in vacuo to give 33 g (97%) of the title compound: mp 103-106 °C.

d) 3-[2-(N,N-Dimethylamino)ethoxy]-4-chloroaniline

To a solution of 4-chloro-3-hydroxyphenylcarbamic acid *tert*-butyl ester (140 mg, 0.57 mmol) in 4:1 DME/water (5 mL) was added dimethylaminoethyl chloride hydrochloride (90 mg, 0.63 mmol) and K_2CO_3 (320 mg, 2.3 mmol). The reaction mixture was heated at reflux for 16 h, at which time it was allowed to cool to room temperature. The DME was removed *in vacuo* and the residue treated with 6 N HCl (2 mL). The resultant mixture was stirred at room temperature

for 2 h, at which time it was diluted with water (5 mL) and washed with EtOAc (5 mL). The aqueous layer was basified with solid K_2CO_3 and extracted with EtOAc (2 x 10 mL). The EtOAc layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give 60 mg (50%) of the title compound.

e) 4-Hydroxy-2-propylsulfanyl-pyrimidine-5-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide

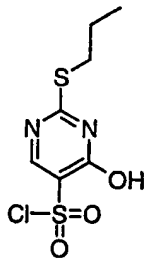
To 4-hydroxy-2-propylsulfanyl-pyrimidine-5-sulfonyl chloride (1.4 g, 5.2 mmol) in pyridine (25 mL) was added 4-chloro-3-(2-dimethylamino-ethoxy)-phenylamine (1.1 g, 5.2 mmol) at rt and stirred for 18 h. The solvent was removed under reduced pressure and the residue was purified by vacuum filtration through a pad of silica gel eluting sucessively with 10% MeOH in CH_2Cl_2 and mixtures of CH_2Cl_2, MeOH and NH_4OH (90:10 1 and 80:20:2, respectively). The solvents were removed from the fractions containing the desired product (LCMS) and the residue was triturated with ether to afford the title compound as an off-white solid; yield 1.0 g (43%): LCMS 447 ($M^+ + H$).

f) 4-Methoxy-2-propylsulfanyl-pyrimidine-5-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide

A mixture of 4-hydroxy-2-propylsulfanyl-pyrimidine-5-sulfonic acid- [3-(2-dimethylamino-ethoxy)-phenyl]-amide (0.40 g, 0.90 mmol) and $POCl_3$ was heated at reflux for 1 h. After cooling to rt, excess $POCl_3$ was removed under reduced pressure and the residue was disolved in MeOH (20 mL). Solid sodium methoxide was added until the solution became strongly basic (pH~11). After stirring for 2 h at rt, saturated aqueous ammonium chloride was added until the pH was slightly acidic. The resuting mixture was concentrated under reduced pressure and the residue purified by HPLC (5-95% CH_3CN / H_2O, 0.1%TFA) to afford the title compound as a white solid; yeild 0.18 g (34%): LCMS (100%) 461 ($M^+ + H$).

Example 1a

Preparation of 4-hydroxy-2-propylsulfany-pyrimidine-5-sulfonyl chloride



a) 2-Propylsulfanyl-pyrimidin-4-ol.

To a mixture of 2-thiouracil (5.0 g, 39 mmol) and K_2CO_3 (5.4 g, 39 mmol) in DMF (200 mL) was added 1-bromopropane (4.8 g, 39 mmol) at rt. After stirring at rt for 18 h, the solvent was removed under reduced pressure. The residue was purified by vacuum filtration through a pad of silica gel eluting successively with 2%, 4% and 10% MeOH in CH_2Cl_2 and a mixture CH_2Cl_2, MeOH and NH_4OH (80:20:2), followed by recrystallization from MeOH / H_2O to afford the title compound as a white solid; yield 3.1 g (43%): LCMS (100%) 171 (M^+ + H).

b) 4-Hydroxy-2-propylsulfany-pyrimidine-5-sulfonyl chloride.

A mixture of 2-propylsulfanyl-pyrimidin-4-ol (3.1 g, 18 mmol) and chlorosulfonic acid (6.0 mL) was heated to150 °C for 3 h. After cooling to rt, excess chlorosulfonic acid was removed under reduced pressure and the residue was poured into a mixture of ice and water and extracted with EtOAc. Removal of the solvent under reduced pressure afforded the title compound as a brown foam; yield 1.4 g (29%): LCMS 269 (M^+ + H)

Example 2

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

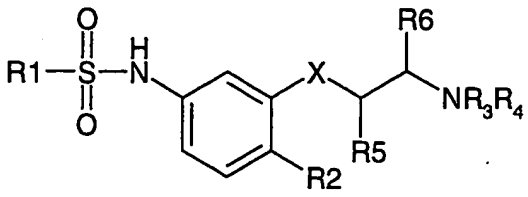
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

R1 is benzofuranyl, benzothiazoyl, benzoxazoyl, benzimidazoyl, oxazoyl, indoyl, triazinyl, imidazoyl, pyrimidinyl, naphthyridinyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl substituted or unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, $CONR_7R_8$, NR_9R_{10}, SC_{1-6} alkyl, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl);

R_2 is hydrogen, halogen, CF_3, CN or C_{1-4} alkyl;

R_3, R_4, R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_5, R_6, R_9, and R_{10} are independently hydrogen or C_{1-6} alkyl;

X is O, S, or CH_2;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein R_1 of the present invention is pyrimidinyl, substituted or unsubstituted by one, two, or three of any of the following: C_{1-6} alkoxy, SC_{1-6} alkyl; R_2 is halogen; R_3 is C_{1-6} alkyl; R_4 is C_{1-6} alkyl; R_5 is hydrogen; R_6 is hydrogen; and X is O.

3. A compound according to claim 1 chosen from the group consisting of: 4-Methoxy-2-propylsulfanyl-pyrimidine-5-sulfonic acid [4-chloro-3-(2-dimethylamino-ethoxy)-phenyl]-amide.

4. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

5. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

6. A method according to Claim 5 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/14412

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 239/46; A61K 31/505
US CL : 544/301; 514/269
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/301; 514/269

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 01/45694 A1 (SMITHKLINE BEECHAM CORPORATION) 19 December 2001 (19.12.2001), see entire document.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2002 (15.07.2002)	22 AUG 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Deepak Rao Felicia D. Roberts for Telephone No. (703) 308-1235

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